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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,059	BALJER ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31* is/are pending in the application.

4a) Of the above claim(s) *17-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/301, 5/15/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-16, in the paper received 1/23/04 is acknowledged. The traversal is on the ground(s) that a search of all of the Groups would not place an undue burden on the Examiner. This is not found persuasive because Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because they lack the same or corresponding special technical features. The special technical features of Groups I-III are biologically, chemically and structurally different products (e.g., antibodies, proteins and DNA) and therefore do not relate to a single general inventive concept and are patentably distinct and independent from one another. The literature search for the three Groups would not be coextensive and it would place an undue burden on the Examiner to search all three groups together.

The requirement is still deemed proper and is therefore made **FINAL**. Claims 17-31 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claim Objections

2. Claims 4, 5 and 9-16 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n).

Specification

3. The disclosure is objected to because of the following informalities:

(a). There are several translation problems with the instant specification. First, the term "oedematose" is used throughout the instant specification and claims However, this is not a term used in the English language. The word "oedematous" (used interchangeably with edematous) means pertaining to, or of the nature of, oedema (edema); affected with oedema (edema). However, the term 'oedematose' is not in any medical dictionary. It appears that Applicants intend to use the term commonly known in the U.S. medical community as 'edema'. The claims and specification should be amended to contain the correct translation and prior art accepted terminology.

The specification should also be reviewed for other translation mistakes. It is noted on page 9, halfway down the page, the word "die" is used instead of 'the'. Also, the word "used" is misspelled as "usefd". The Examiner does not have time to review the specification word by word, line by line. It is suggested that Applicants review the specification for accuracy and make the appropriate changes. A substitute specification in proper idiomatic English and in compliance with 37 CFR 1.52(a) and (b) may be submitted. The substitute specification filed must be accompanied by a statement that it contains no new matter. However, if Applicants prefer they may make the changes line by line.

Appropriate correction is required.

(b). The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or
REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)
(e) BACKGROUND OF THE INVENTION.
(1) Field of the Invention.
(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(f) BRIEF SUMMARY OF THE INVENTION.
(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(h) DETAILED DESCRIPTION OF THE INVENTION.
(i) CLAIM OR CLAIMS (commencing on a separate sheet).
(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Specification

4. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required:

Original claims 3 and 8 recite that the terminal tag is no larger than 1 kDa. The instant specification recite that the size of the terminal tag is "preferably **5** kDa, as a maximum, and more preferably is 5 kDa". See page 2, last 3 lines. Nowhere in the

specification could the size '1 kDa" be found. The specification should be amended to provide proper antecedent basis matter for the claimed subject matter. Correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 are vague and indefinite because it is unclear what is meant by the term "sub-genic Stx2e fragment". What does the term 'sub-genic" mean? Additionally, a 'fragment' reads on as little as one amino acid. There is no function tied to this fragment. The claim is also vague and indefinite due to the phrase "the size of which corresponds to the size of the fragment or a fraction of the fragment". This description fails to set forth a size. A fraction can be as small as one amino acid.

Claim 2 is vague and indefinite because it is unclear what is meant by the term "sub-genic". Clarification is requested.

Claims 3 and 8 are vague and confusing because it is unclear if the claims intend to recite that the terminal tag is no larger than 1 kDa. The wording of the claims is unclear. Additionally, the instant specification recite that the size of the terminal tag is "preferably **5** kDa, as a maximum, and more preferably is 5 kDa". See page 2, last 3 lines. Nowhere in the specification could '1 kDa" be found. Clarification is requested.

As stated above, claims 4 and 5 are improper multi-dependent claims since a multi-dependent claim cannot depend from another multi-dependent claim. Correction is required.

Claims 5 and 10 are vague and indefinite because it is unclear how the recombinant fusion proteins has "a plurality of crosslinked fusion proteins". This is unclear. What does this mean? Is this a huge protein cluster of various recombinant proteins? Clarification is requested.

Claims 6-16 are vague and indefinite due to the parentheticals surrounding the term 'vaccine'. The use of the parentheticals around the term make it unclear whether or not the composition claim is, indeed, a vaccine. Additionally, the use of the term 'substance' is unclear. It is not clear what 'substance composition' means. It is suggested that Applicants amend the claims to recite a "vaccine composition" or merely a "vaccine".

Claim 6 is vague and indefinite due to the phrase "for various applications in conjunction with the oedematose of animals, particularly those of mammals, specifically pigs". Is the claim limited to vaccines for pigs? The use of the term "particularly" followed by the term "specifically" makes it unclear. Also, it is unclear what "for various applications in conjunction with the oedematose of animals" means. What are the various applications and how are they in conjunction with oedematose? Do Applicants intend to claim "A vaccine for treating or preventing odematose in mammals...."? If so, this should be made clear. Correction is required.

Claims 6 and 14 use the term "oedematose". However, this is not a term used in English. The word "oedematous" (used interchangeably with edematous) means pertaining to, or of the nature of, oedema; affected with oedema. However, the term 'oedematose' is not in any medical dictionary. It appears that Applicants intend to use the term commonly known in the U.S. medical community as 'edema'. The claims and specification should be amended to contain the correct translation.

Claim 6 recites the limitation "the fragment B". There is insufficient antecedent basis for this limitation in the claim. The preceding portion of the claim only recites "a sub-genic fragment of the 2e Shiga toxin". It does not recite that this fragment is the B-subunit. Accordingly, there is no antecedent basis for "**the** fragment B" in the last line of the claim.

Claim 7 is vague and indefinite because it is unclear what is meant by the term "sub-genic".

Claim 8 is indefinite for being in improper Markush format. The Office recommends the use of the phrase "selected from the group consisting of...".

Claims 11 and 13 are vague and indefinite because it is unclear how the "one additional antigen or several additional antigens" are associated with the recombinant protein. Are they attached or are they in a mixture? Clarification is requested.

In claim 13, the term "disactivated" is unclear. Do Applicants mean 'inactivated"? If so, correction is required. Claim 13 is also vague and confusing because it recites cultures of Actinobacillus pleuropneumoniae, Haemophilus parasuis, ..., Porcine

Reproduction and Respiratory Syndrom virus, influenza virus, Pseudorabies virus, etc.. These pathogens would be toxic to a host. Clarification is required.

Claim 13 is vague and confusing because it is unclear what the 2E Stx-IIe fragment of the 2e Shiga toxin is in reference to. Claim13 recites the limitation "the 2e Stx-**IIe** fragment". There is insufficient antecedent basis for this limitation in the claim as none of the preceding claims recite a Stx-IIe fragment.

Claim 13 is vague and indefinite because it is unclear what is encompassed by "an immunogenic amount for the vaccination of pigs against oedematose of the pigs or against the oedematose of the pigs and other viral and/or bacterial infections. The specification fails to teach such an amount. Accordingly, the amount cannot be quantified.

Claim 14 is vague and indefinite because it recites "compositions and amounts such that if the pigs are vaccinated sequentially or simultaneously they immunize them against oedematose of the pigs or against the oedematose of the pigs and other viral and/or bacterial infections". First, it is unclear who "they" is in reference to. Second, the preceding claims do not require the use of pigs thereby making use of the phrase "the pigs" unclear.

As stated above, claims 9-16 are improper multi-dependent claims since a multi-dependent claim cannot depend from another multi-dependent claim. Correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 6-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to vaccines for various applications in conjunction with the oedematose of animals, particularly those of mammals, specifically pigs, having a sub-genic fragment of the 2e Shiga toxin in fusion with a terminal tag the size of which approximately corresponds to the size of the fragment or a fraction of the fragment B. The use of additional antigens are taught, as well as the use of emulsion or and/or adjuvants. Claim 14 specifically recites that the vaccine compositions and amounts are such that if the pigs are vaccinated sequentially or simultaneously they immunize them against oedematose of the pigs or against the oedematose of the pigs and other viral and/or bacterial infections.

The instant claims are broadly drawn to *any* size fragment from Stx2e including fragments from both the A and B subunits. Additionally, the independent claims allow for *any* terminal tag. However, the inventive concept appears to be a recombinant fusion protein comprising the B subunit from the 2e Shiga toxin in fusion with an amino terminal His tag which is no larger than 5 kDa. Independent claims 1 and 6 are broadly written to encompass recombinant fusion proteins comprising Stx2eB and Gutathion S

transferase, as well as any Stx2e fragments linked to any hapten. The instant specification recites that the discovery of the Stx2eB-His fusion protein appeared to eliminate immunological problems encountered with Stx2eB-GST and Stx2eB-His has the advantage of being able to be used as a vaccine. The claims should reflect this inventive concept.

Further, the specification is not enabled for vaccines which treat or prevent oedematose [edema] or for any 'applications in conjunction with the oedematose [edema] of animals', is it enabled for vaccines for treating or prevent *E.coli* infection. The specification has provided results which demonstrate the immunization of young pigs/piglets with will raise an immune response against the Stx2e shiga toxin and will not harm the piglets. However, no challenge experiments were done which are necessary to enable the use of the fusion protein as a 'vaccine' which requires a protective effect. The demonstration that the fusion protein can generate antibodies in young pigs is not sufficient to enable its use as a vaccine. The specification has not demonstrated that the recombinant vaccines can prevent edema upon exposure to the 2e Shiga toxin. The bacterial vaccine art is highly unpredictable. Most immunogens which can raise antibodies against a bacterial antigen or toxin are not able to induce a protective immune response. For enablement as a vaccine, challenge experiments must be provided which demonstrates the vaccine's efficacy. It is also noted that the vaccines recited in claims 6-16 read on human vaccines, i.e, mammals. However, in humans the Stx2e toxin causes a lethal systemic vascular disease. Edema disease is a disease of young pigs caused by host-adapted *E.coli* that produces a variant of Stx2,

called Stx2e. The specification provides no results on humans or any indication that the vaccine is intended for humans. Additionally, the specification fails to provide any results with any fusion proteins other than the full B subunit of Stx2e linked to a His terminal tag. The specification is not enabled for vaccines or pharmaceutical/immunogenic compositions comprising *any* size fragment from Stx2e (which include fragments from either the A and B subunits) or any terminal tag up to size of the fragment as the independent claims currently read. It is suggested that the claims be limited to "pharmaceutical/immunogenic compositions comprising a recombinant fusion protein comprising the B subunit from the 2e Shiga toxin in fusion with an amino terminal His tag which comprises six histidines". specification is non-enabling, since one skilled in the art would not be able to make and use those sequences without undue experimentation.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-16 are rejected under 35 U.S.C. 102(b) as being anticipated by O'Brien et al (WO 98/11229, March 19, 1998).

O'Brien et al disclose histidine-tagged shiga toxin fusion proteins. O'Brien et al teach that histidine tagging greatly facilitates purification of Shiga toxins. The use of the histidine-tagged fusion proteins for generating an immune response against infection or

transmission by bacteria expressing Shiga toxin is also taught. See page 1, lines 15-21. O'Brien teach that Shiga toxin includes any toxin in the Stx1 or Stx2 group. See page 3, lines 9-10. Stx2e is specifically taught as a member of the Stx2 group. See page 3, lines 1-5. O'Brien et al teach that smaller fragments of the Shiga toxin tagged to His may be used. See page 6, lines 16-29. The reference teaches that a smaller fragment might may be selected to enhance stability of the combined fusion protein. Page 17, lines 18-29 teach that various proteins, haptens and antigens from bacteria, rickettsiae, fungi and parasites may be added to the fusion protein. The use of adjuvants are taught. The instant claims are not limited solely to a Stx2e B subunit and a His_6 tag and therefore are anticipated by the reference. Lastly, the phrase "vaccines for various applications in conjunction with the oedematose of animals, particularly those of mammals, specifically pigs" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

11. Claims 1-3 and 6-8 and are rejected under 35 U.S.C. 102(b) as being anticipated by any one of Franke et al (Vet Microbiol. 1995. 43: 41-52), Acheson et al. (Infect. Immun. 1995. 63(1) : 301-8) or Wieler et al (Lecture read at the 21st DVG congress at Bad Nauheim March 1995).

Claims 1-3 and 6-8 do not specify the properties of the terminal tag of the fusion protein.

Franke et al teach a recombinant fusion protein comprising the B subunit of Stx2e and GST (glutathion S transferase). GST is being interpreted to read on the 'terminal tag'. Franke teach that the recombinant SLT-II B subunit may be a possible candidate for a vaccine.

Acheson et al teach that the B subunit of the Stx2e toxin can induce the formation of toxin-neutralizing antibodies after parental application. The Stx2e was expressed as a fusion protein with maltose binding protein. Maltose binding protein is broadly being interpreted as the 'terminal tag'.

Weile teach that the recombinant fusion protein from a fragment of the Stx2eb subunit and the Glutathion S transferase was used to monitor the antibody response of an outbreak of edema disease in piglets. The reference teaches that the fusion protein is good candidate for a potential vaccine. The GST is being broadly interpreted as a 'terminal tag'.

Lastly, the term "vaccine" and the phrase "vaccines for various applications in conjunction with the oedematose of animals, particularly those of mammals, specifically pigs" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The instant claims are not limited solely to a Stx2e B subunit and a His_6 tag and therefore are anticipated by the references.

12. Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile

transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

J Graser 3/31/04

Jennifer Graser
Primary Examiner
Art Unit 1645